**REMARKS/ARGUMENTS**

Upon entry of this amendment, claims 20, 21, 28 to 35, 37, 41, 42, 46 and 52 to 58 are pending in the application. Claims 29, 34 and 37 have been amended for the purpose of advancing the case toward allowance and the amendments should not be viewed as acquiescence to any of the Examiner's rejections. Claims 52 to 58 have been added. New claims 52 to 54 and amended claim 34 are directed to cytokines. The specification provides a number of examples of cytokines at, for example, page 31, lines 2 to 8 where, for example, erythropoietin, G-CSF, GM-CSF and interferon are disclosed. Claims 55 and 56 are directed to detectable levels of exogenous protein. Support for these claims can be found, for example, in Example 5 at page 36 of the specification which discloses detection of exogenous protein beta-lactamase in egg white of a transgenic chicken. Claims 57 to 58 are directed to eggs with an intact egg shell. Support for these claims is at least inherent in the specification since when the egg containing the heterologous protein is laid by the chicken it is understood that the egg shell is intact.

Entry of the amendment, reconsideration of the rejection, and allowance of claims 20, 21, 28 to 35, 37, 41, 42, 46 and 52 to 58 are respectfully requested.

The Examiner rejects the claims under 35 USC 102(b) as being anticipated by Bosselman et al, US Patent No. 5,162,215 (Bosselmen). The Examiner indicates that Bosselman teaches the making of transgenic chickens and eggs thereof wherein the egg contains a desired protein such as human serum albumin, alpha 1-antitrypsin, blood clotting factors (factor VII) and hematopoietic growth factors (EPO, G-CSF and LGF) and that therefore, Bosselman anticipates the invention as claimed. Applicant traverses the rejection.

There is no evidence or even a suggestion presented in Bosselman that the methods of Bosselman led to the production of exogenous proteins in the egg of a chicken. Without supporting data, it is incorrect for the Examiner to assert that the methods of Bosselman could lead to the deposition of a heterologous protein in the egg of a transgenic chicken. See, for example, paragraph 7 of the accompanying Declaration of Dr. Ann Gibbins (Gibbins Declaration), a top researcher in the field of avian transgenesis at the time of the Bosselman filing, where it is stated that:

> Based upon my own professional experience and knowledge, obtaining heterologous protein in the egg of a chicken is a complex task and such an accomplishment cannot be taken as fact without supporting data.

Bossleman presents data showing use of an REV vector to produce 15 day-old embryos having recombinant protein (cGH) present in their serum, as determined by radioimmunoassay and western blot analyses (column 13, lines 50 to 60 and Table I). Bosselmen also states that analysis of hatched chickens supports the results obtained with the embryos (column 14, line 15 to 16). In addition, Bossleman reports the successful germline transmission of the REV vectors resulting in G1 transgenic birds (see Example 4). At no point does Bosselman present data or even suggest that the recombinant protein (cGH) was present in a transgenic chicken egg. With all the assays, analyses and work that would have been required for the production of G1 transgenic birds reported in Bosselman, it would have been a trivial matter to test for the presence of the exogenous cGH in the eggs produced by the transgenic birds and would expect that such analyses would have been performed. In support of this assertion, see paragraph 8 of the Gibbins Declaration where it is stated that:

> I believe that if researchers were able to show production of a heterologous protein in the serum of transgenic chickens by western blot and/or radioimmunoassay, as was the case in the Bosselman Patent, little additional effort would have been required to test the contents of the transgenic chicken eggs for the presence of the same heterologous protein.

At the time of Bosselman it was well known to skilled artisans in the field of avian transgenesis that it would be a substantial technological advance to produce transgenic chickens which could lay eggs containing an exogenous protein. See, for example, paragraph 4 of the Gibbins Declaration where it is stated that:

> Heterologous protein deposition into transgenic chicken eggs would have been considered a most significant accomplishment at the time of filing the Bosselman Patent. Pursuit of this type of protein engineering was very much at the forefront of avian transgenesis research in the 1980s and into the 1990s.

The importance of successfully producing heterologous protein in a chicken that is deposited into the egg was no doubt apparent to Bosselman as it was to other practitioners in the field at the time of the Bosselman filing. That is, speculation for this type of heterologous protein production was common place in the field of avian transgenesis at the time of the

Bosselman filing. See, for example, Perry et al (US Patent No. 5,011,780, filed June 1988) which states at column 17, lines 6 to 13:

> Furthermore, the insertion of genes for novel proteins into the avian germ line is a potentially valuable technique for the production of biomedically important proteins in egg white. The high reproductive capacity of the domestic fowl gives it an advantage over other farm animals in this technological field. A hen matures in 6 months and is capable of producing some 300 eggs in the first year of lay.

Also, see for example, the second half of paragraph 4 of the Gibbins Declaration where it is stated that:

> In fact, the idea of producing heterologous proteins such as pharmaceutical proteins in the eggs of transgenic chickens was not suggested for the first time in the Bosselman Patent. See, for example, the last sentence of the Summary of my paper presented at The Thirty-Seventh Annual National Breeders Roundtable, dated May 5, 1988, entitled Gene Constructs for Testing Transgenic Poultry, and also the full paragraph on page 19 of this paper where a general design for the production of heterologous proteins in transgenic chicken eggs is discussed. Similar material was presented by me or my graduate students at other scientific meetings in Japan, England and Canada, prior to Sept. 22 1988.
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> A copy of Thirty-Seventh Annual National Breeders Roundtable paper cited by Dr. Gibbins is included with this response.

Moreover, even during the pendency and after the issuance of Bosselman, exogenous protein production in eggs of transgenic chickens was stated by experts in the field of avian transgenesis to be a potential application for avian transgenesis, indicating that prior science including Bosselman did not solve the challenge of producing exogenous proteins in the eggs of transgenic chickens. See, for example, Shuman Experientia (1991) vol 47, copy included with this response, last full paragraph at page 903 where it is stated that:

> Gene transfer may also make it possible to use the chicken as a bioreactor for the production of pharmaceuticals and other proteins. At least two possibilities are envisioned both involving the hen's remarkable reproductive system. One idea is to express the pharmaceutical gene in either the oviduct of the hen so that the protein product is incorporated into the albumen of the egg[43]. Alternatively, the gene could be expressed in the liver and manipulated in such a way that it will be incorporated into the egg yolk (Gibbins, personal communication). The ultimate

> goal would be to provide a new manufacturing system that could produce bioproteins at costs which are lower than mammalian or bacterial cell culture while providing a correctly processed, biologically active product. Because of the high reproductive rate and relatively short generation interval of chickens and high protein ratio in eggs, chickens may have an advantage over mammals, including rabbits, mice, goats, sheep and cattle that are currently being tested as possible bioprotein production systems (see Wilmut et al., this review).
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> [43] Shuman Genetic Engineering, in: Poultry Breeding and Genetics, pp. 585-598. Ed. R. D. Crawford. Elsevier, Amsterdam 1990.

Also see the last full paragraph at page 418 of the review article entitled "Transgenic Chickens - Methods and Potential Applications", Sang (1994) TIBTECH vol 12 p 415-420 (Sang), copy included with this response, where it is stated that: "One of the potential major uses for transgenic technology in chickens is the production of foreign proteins in hens' eggs." (underlining added by applicant for emphasis).

In both the Sang and Shuman articles, production of transgenic chickens by a variety of methods is reported with specific mention of the Bosselman work being made in both articles. See, for example, the *Retroviruses as gene delivery systems* section of Shuman beginning at page 898 thru page 902 and the **Genetic manipulation before lay** and **Transfection of the laid-egg embryo** sections of Sang at page 416. In spite of the reported production of germline transgenic chickens in these articles, production of foreign proteins in the eggs of transgenic hens is described only as a potential application for avian transgenesis.

Why the transgenic chickens of Bosselman did not produce eggs containing the exogenous proteins could be due to a variety of reasons such as those discussed at paragraph 6 of the Gibbins Declaration where it is stated:

> The deposition of proteins into eggs is not universal or automatic and depends on many factors. For example, in deposition in the egg yolk specific carrier molecules and receptors are typically required that can bind to and shuttle the transported proteins into the growing ovum. Deposition into egg white requires among other things the heterologous gene expression being under the control of functional gene expression regulating elements that provide for expression in oviduct tissue, specifically in tubular gland cells. The Bosselman Patent does not postulate initial deposition of heterologous proteins by either route and provides no evidence from their work of heterologous protein being present in any portion of the egg.

In summary, as stated in the Gibbins Declaration at paragraphs 9: "I believe that without evidence to the contrary, there is no reason to believe the transgenic chickens described in the Bosselman Patent produced any detectable level of heterologous protein packaged into eggs." Therefore, since Bosselman did not disclose the making of eggs of transgenic chickens containing exogenous protein, applicant requests that the rejection be withdrawn.

The Examiner rejects claims 34 to 37 under 35 USC 102(b) as being anticipated by Boldt (US Patent No. 4,296,134). The Examiner states that claims 34 to 37 are drawn to chicken egg white comprising a protein exogenous to the egg white and that given the broadest reasonable interpretation, the cited art anticipates a chicken egg white comprising exogenous protein. Applicant believes that the Examiner meant to say "drawn to chicken egg white comprising a pharmaceutical protein" and applicant will address the rejection accordingly. Applicant traverses the rejection. However, in an effort to facilitate prosecution of the application the independent claim 34 has been amended to recite "a cytokine" in place of "a pharmaceutical protein" and claim 37 has been amended to delete lactoferrin.

The Examiner rejects claim 29 under 35 USC 103(a) as being unpatentable over Bosselman in view of Sekellick, US Patent No. 5,885,567 (Sekellick). The Examiner states that it would have been obvious to one of ordinary skill in the art at the time of filing to modify the invention of Bosselmen by substituting a cytokine with interferon in view of Sekellick. Applicant traverses the rejection and disagrees with the Examiner since, for example, Bosselman does not enable the production of a transgenic avian that produces eggs containing exogenous proteins and, therefore, the cited references cannot be used to make obvious claim 29.

In conclusion, applicant has shown that pending claims 20, 21, 28 to 35, 37, 41, 42, 46 and 52 to 58 meet the requirements for patentability and that in view of the cited references the claims are not anticipated under 35 USC 102 and are nonobvious under 35 USC 103. Therefore, the presently pending claims are allowable and applicant respectfully requests the Examiner to pass the above-identified application to allowance.

If any issues remain to be addressed in this matter, which might be resolved by discussion, the Examiner is respectfully requested to call applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

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